REVIEW ARTICLE

The Clinical Implications of Blood Adiponectin in Cardiometabolic Disorders

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Adipose tissue is now accepted by the scientific and medical community to be a genuine endocrine organ, in addition to its classical role as an energy store. Adiponectin is one of the many adipocytokines that are secreted almost exclusively by adipose tissue. Alteration in blood adiponectin concentrations has been linked to many human diseases in numerous cross-sectional and prospective studies. In this review, we describe briefly the biological effects of adiponectin as revealed by basic scientific investigations. We also summarize the principles of blood adiponectin assays. Overall, lower blood adiponectin concentration is found in subjects with obesity, type 2 diabetes mellitus, dyslipidemia, and hypertension. These medical conditions are components of the metabolic syndrome and major risk factors for accelerated atherosclerosis. Plasma adiponectin levels are also expected to be lower in subjects with cardiovascular diseases, such as coronary artery disease, ischemic stroke and peripheral artery disease. Congestive heart failure (CHF) and cardiac arrhythmia are common end points in cardiovascular diseases. Surprisingly, higher blood adiponectin levels are frequently reported to predict mortality associated with CHF. Few human data regarding adiponectin and cardiac arrhythmia are available. Higher blood adiponectin level has been documented only in atrial fibrillation. We also summarize data on the role of the high molecular weight (HMW) isoforms of adiponectin and the effects of clinical treatment on the levels of total or HMW adiponectin. Whether adiponectin is a risk marker or a risk factor for the diseases reviewed in this article, and in many other human diseases, and their detailed pathogenic links awaits further investigation. [*J Formos Med Assoc* 2009;108(5):353–366]

Key Words: adiponectin, arrhythmia, atrial fibrillation, cerebrovascular disease, coronary artery disease, diabetes, dyslipidemia, heart failure, hypertension, metabolic syndrome, obesity, peripheral vascular diseases, stroke

Fat Hormone

Obesity has become a global epidemic in children and adults, and is considered to be the root cause of many metabolic diseases that we face today.[1] Through advancing our understanding of the pathogenesis of obesity, we no longer view adipose tissue as a simple fat reservoir for energy storage. Instead, adipose tissue is now considered an endocrine organ, actively regulating energy balance and many other physiological functions.[2] The crucial evidence leading to the formation of this concept was the discovery of leptin.

More than 40 years ago, monogenic obesity and diabetes mouse models, obese (*ob*) and diabetes (*db*), were identified.[3,4] These two models were

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demonstrated to harbor two spontaneous recessive mutant alleles. Although they share similar syndromes of hyperphagic obesity with prominent diabetes and endocrine dysfunction, they are in fact caused by two different genes.[5] The parabiosis experiments conducted by Coleman et al provided insight into the underlying mechanisms.[6,7] Connecting the blood circulation of *ob*/*ob* mice with that of wild-type or *db*/*db* mice led to significant weight loss in the *ob*/*ob* animals, while connecting the circulation of *db*/*db* mice with that of *ob*/*ob* or wild-type mice exerted no effect on the *db*/*db* animals. These findings indicate that a circulating factor that causes weight loss is missing in *ob*/*ob* mice, while possibly the receptor for the factor is lacking in *db*/*db* mice. This circulating factor, a 16-kDa peptide hormone, was later discovered by positional cloning of the *ob* gene in mice in 1994.[8] Since the factor promoted weight loss in *ob*/*ob* mice, it was termed leptin, which was derived from "leptos", the Greek for thin.[9] Soon thereafter, the leptin receptor was also cloned in 1995.[10] The leptin receptor is exactly what is missing in *db*/*db* mice. Leptin therefore became the first example of the fat hormones, or the so-called adipocytokines or adipokines, which are produced mainly by the adipose tissues and have significant systemic effects. A comprehensive review of leptin is beyond the scope of the present article. Readers interested in this are advised to read some recent reviews.[11,12]

Among the adipocytokine family, adiponectin, the second example of the fat hormones, has drawn much attention recently from researchers seeking its biological and clinical implications.[13]

Basic Science of Adiponectin

In the mid-1990s, four independent Japanese or American groups isolated adiponectin (also known as Acrp30/adipoQ/apM1/GBP28) by using diverse techniques.[14–17] Adiponectin is secreted primarily from mature adipocytes. It is a 30-kDa molecule that contains a 20-residue amino-terminal signal sequence, a variable region, a collagenous domain and a carboxy-terminal globular domain.[18] Adiponectin circulates in the blood in higher-order structural forms and at a relatively high concentration compared with the other peptide hormones.[17] These multimeric forms identified by different methods (such as gel filtration chromatography, gel electrophoresis or Western blotting) include trimeric (low molecular weight, LMW), hexameric (middle molecular weight, MMW), and even high molecular weight (HMW) complexes.[17,19] Although some studies have proposed that the ratio of the HMW to other forms may serve as a better indicator of metabolic disorders,[19–22] the majority of studies that have linked adiponectin with metabolic diseases have used assays for total adiponectin.

One of the effects of adiponectin on energy balance is mediated by an increase in β-oxidation of fatty acids in skeletal muscles.[23] In mice, administration of the protease-generated globular head domain of adiponectin decreases dramatically the level of plasma free fatty acids.[23] It has also been demonstrated in mice that injection of adiponectin can reduce plasma glucose levels and improve insulin sensitivity.[24,25] The repression of hepatic glucose output is accomplished through lowering the mRNA expression of hepatic gluconeogenic enzymes, such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.[26] Besides, studies that have utilized adiponectin knockout mice have shown that these mice are inclined to diet-induced insulin resistance and glucose intolerance.[27,28] In *ob*/*ob* mice, transgenic adiponectin keeps the animals from developing insulin resistance and hyperglycemia.[29]

Substantial evidence in animal studies has shown that adiponectin may also exert advantageous effects on the cardiovascular system. In adiponectin knockout mice, hypertension induced by treatment with high-salt diet can be alleviated by adenovirus-delivered adiponectin.[30] In adiponectin-deficient mice, pressure overload induces concentric cardiac hypertrophy and mortality.[31] Moreover, adiponectin supplementation reduces lipid accumulation on the vascular wall,[29,32] attenuates neointimal proliferation[33]

and thrombus formation,[34] and improves angiogenic repair.[35]

In 2003, Yamauchi et al identified adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2).[36] These receptors, predicted to contain seven transmembrane domains, are mainly found in skeletal muscle, liver, and pancreatic β cells. AdipoR1 is expressed extensively in skeletal muscle, while AdipoR2 is distributed mostly in liver. Additionally, functional differences between AdipoR1 and AdipoR2 have been demonstrated.[37] While AdipoR1 is involved in the AMP-dependent protein kinase (AMPK) signaling pathway, AdipoR2 is associated more with the peroxisome proliferator activator receptor (PPAR)-α pathway.[37] Besides the above-mentioned pathways, adiponectin stimulates various signaling pathways. For example, adiponectin activates p38 mitogen-activated protein kinase (MAPK) and c-*jun* N-terminal kinase (JNK) in osteoblasts, which enhances cell proliferation and differentiation.[38] In human umbilical vein endothelial cells, adiponectin inhibits the activation of IκB kinase (IKK) induced by tumor necrosis factor (TNF)-α or high glucose, which supports its anti-inflammatory role.[39] In vascular endothelial cells, adiponectin stimulates production of nitric oxide through phosphatidylinositol-3-kinase-dependent pathways.[40] The regulation of adiponectin expression and its post-receptor signaling has been discussed in some recent review articles.[13,41]

Implications of Plasma Adiponectin in Human Cardiometabolic Disorders

Assays for blood adiponectin

For determination of adiponectin levels in peripheral circulation, many immunometric systems, such as radioimmunoassay (RIA) and ELISA, have been developed and have been available commercially for many years. The pioneer development of ELISA was achieved by Arita et al from Matsuzawa's laboratory and has had many applications in clinical research.[42] For ELISA measurement of adiponectin, the adiponectin multimers in the biological samples are converted to monomers or dimers by treatment with SDS at high temperature or at pH 3.0–3.5.[42,43] The calibration curve is obtained by using recombinant adiponectin or dimeric adiponectin as a calibration standard.[42,43] If a particular molecular weight form is of special interest, two kinds of proteinase can be used to digest selectively the adiponectin multimers.[43] Protease A (from *Aspergillus oryzae*), which digests LMW adiponectin can be utilized in the measurement of MMW and HMW forms. In contrast, protease K (from *Tritirachium album*), which digests LMW and MMW adiponectin can be applied to the evaluation of the HMW form. Thus, by combination, the concentration levels of each form may be obtained. For interested readers, a more comprehensive discussion can be found in some recent papers.[19,43–47] In the following discussion, whenever adiponectin is mentioned, total adiponectin is implied unless indicated otherwise. Previous studies have shown different results with regard to whether HMW adiponectin complexes are the main component related to its biological effects. This will be reviewed in this article. Furthermore, since the amount of the HMW form is so closely related to the total adiponectin level, some authors have reported that measurement of the HMW complexes does not provide additional information.[48]

The association between plasma adiponectin levels and various diseases has been demonstrated in numerous human studies.[49–51] In this review, we will limit our discussion to human metabolic and cardiovascular disorders. Human genetic studies of adiponectin and its receptors have also revealed important implications of adiponectin in human diseases.[52–54]

Plasma adiponectin and obesity

Obesity provided the first link between human disease and plasma adiponectin levels.[42] In the very first report of ELISA for plasma adiponectin, Arita et al demonstrated the paradoxical association between body mass index (BMI) and plasma adiponectin levels.[42] They also showed that females in general had higher plasma adiponectin than

males. In addition, body fat distribution was found to be influential. Intra-abdominal fat mass is more related to adiponectin concentration than subcutaneous fat is.[55–57] Although adiponectin has been related closely to obesity in cross-sectional studies, lower plasma adiponectin is unlikely to be the cause of obesity. On the contrary, hypoadiponectinemia is probably the result of obesity. In fact, in a prospective human study, low plasma adiponectin was not shown to predict future body weight gain.[58] Recently, we have reviewed extensively this issue.[13]

Lifestyle modification to reduce body weight has been shown to increase plasma adiponectin levels in type 2 diabetes mellitus (T2DM) as well as in non-diabetic subjects.[59] Exercise itself, without significant weight reduction, may not have a major influence on plasma adiponectin levels.[60,61] Anti-obesity pharmacotherapy may also increase plasma adiponectin levels. Modest weight reduction supplemented with orlistat, a pancreatic lipase inhibitor, increases plasma adiponectin.[62,63] Sibutramine, a neurotransmitter reuptake inhibitor, reduces weight with or without increasing plasma adiponectin.[62,64,65] Rimonabant, an endocannabinoid receptor blocker, reduces weight, improves metabolic profiles and increases plasma adiponectin.[66] Among severely obese subjects, anti-obesity surgery results in significant weight reduction and metabolic benefits, accompanied by increased plasma adiponectin levels.[67,68] In contrast, contradictory results regarding the effects of liposuction on obesity-related metabolic abnormalities and plasma adiponectin levels have been reported.[69,70] In summary, we can conclude that any clinical measure that gives rise to significant weight reduction and improvement in insulin sensitivity can, without doubt, increase the blood concentration of adiponectin.

In more recent studies, the relationship between obesity and different isoforms of adiponectin has been addressed. It appears that total and HMW adiponectin isoforms are more related to obesity and visceral fat.[71,72] However, some authors have not observed the significance of HMW adiponectin in obesity.[73] Weight reduction also appears to increase total adiponectin, HMW adiponectin and the ratio of HMW to total adiponectin.[74,75]

Plasma adiponectin and diabetes mellitus

The circulation levels of adiponectin are lower in T2DM,[59,76] and in insulin-resistant states.[76,77] The Pima Indians of Arizona, USA, are a special population that is prone to obesity and T2DM. A longitudinal study has revealed that subjects with high adiponectin concentrations are less likely to develop T2DM.[78] Research on Japanese and other ethnic groups has implied that lower adiponectin levels are associated with increased future risk of developing insulin resistance, impaired glucose metabolism and diabetes.[79–85] Reduction of HMW adiponectin isoforms is associated with the risk of insulin resistance and T2DM.[86–89]

In contrast to that in T2DM, the plasma concentration of adiponectin tends to be higher in type 1 diabetes mellitus (T1DM).[90–93] Even HMW adiponectin is increased in T1DM.[94] However, in one study, the plasma adiponectin levels did not predict the occurrence of T1DM in autoantibody-positive relatives.[95] The controversy regarding whether the increased plasma adiponectin concentration is caused by or related to co-existing microvascular complications, especially nephropathy, remains unresolved.[92,94,96–99]

Lifestyle modification with significant weight reduction has been shown to enhance plasma adiponectin concentration in T2DM, as discussed above.[59,100] Treatment of T2DM with oral antidiabetic agents may also alter blood concentrations of adiponectin. In general, insulin secretagogues, including sulfonylureas and meglitinides,[101,102] do not clearly increase plasma adiponectin levels, except for glimepiride and repaglinide.[103,104] The rare exception of glimepiride might be explained by its long-claimed insulin-mimetic or insulin-sensitizing effects.[105] However, how repaglinide increases plasma adiponectin remains unknown.[106] Metformin does not appear to have a major effect on plasma adiponectin concentration in T2DM or in polycystic ovary syndrome, even though some studies have shown a significant increase after treatment.[102,107,108] The α-glucosidase inhibitor

acarbose induced a small but significant rise in serum adiponectin in only one study.[109] In contrast, thiazolidinediones (TZDs), such as rosiglitazone and pioglitazone, increased plasma adiponectin in many human studies.[101,110] This is related to their insulin-sensitizing effects via PPARγ2 activation in the adipose tissue. It has been shown that some of the benefits of TZDs may be exerted mainly through improving the levels of HMW adiponectin complexes.[111,112] So far, there have been no human studies of dipeptidyl protease-4 inhibitor or glucagon-like peptide-1 (GLP-1)-based therapy in relation to adiponectin. However, we believe, with its effects on body weight, GLP-1-based therapy should more or less increase plasma adiponectin levels. A few studies of insulin treatment have indicated that there might be no significant change in blood adiponectin with chronic insulin treatment.[113–115] Some other studies have found acute suppressive effects of insulin on adiponectin levels in human studies.[116–119] However, others have found no effect on plasma adiponectin levels in patients with acute hyperinsulinemia.[120]

Plasma adiponectin and dyslipidemia

Low blood levels of adiponectin are also related to dyslipidemia.[77,121,122] A positive correlation has been found between adiponectin levels and high-density lipoprotein (HDL)-cholesterol, while an inverse relationship with triglycerides and apolipoprotein (Apo) B has been demonstrated.[77,121–124] Furthermore, HMW adiponectin was correlated with the decrease in large triglyceride-rich very-low-density lipoprotein (VLDL) and in small low-density lipoprotein (LDL), but with the increase in large buoyant LDL particles, accompanied by increased LDL particle size, and the increase in large HDL and HDL particle size.[125]

Statins are the mainstream pharmacotherapy for hypercholesterolemia, specifically high LDL-cholesterol. Treatment with statins in humans does not significantly alter plasma adiponectin levels in general.[126–129] The intestinal cholesterol transporter inhibitor ezetimibe is available in clinical practice for treating hypercholesterolemia. Treatment with ezetimibe also does not alter plasma adiponectin levels.[130] Fibrates are used to treat hypertriglyceridemia. The effects of fibrates on plasma adiponectin are inconsistent. Some studies have shown an adiponectin-raising effect,[131,132] while others have not found any effect.[133,134] One report has suggested that fibrates do not increase total plasma adiponectin, but rather increase the HMW portion.[135] Nicotinic acid lowers triglycerides, LDL-cholesterol and raises HDL-cholesterol. Extended-released nicotinic acid increases plasma adiponectin, preferentially the HMW forms.[136–138] Chronic treatment with acipimox, a lipolysis inhibitor similar to nicotinic acid, does not alter plasma adiponectin level.[139,140] However, the acute effects of acipimox are inconsistent. One study has shown reduced plasma adiponectin levels,[141] but another has shown no change in plasma adiponectin concentration after acute administration.[117]

Plasma adiponectin and hypertension

The inverse relationship between adiponectin level and blood pressure has been investigated in many previous studies,[142–145] and re-enforced recently by a 5-year prospective study.[146] Chow et al found that hypoadiponectinemia can serve as a powerful predictor for future development of hypertension, even after adjustment for well-known risk factors, including sex, age and BMI.[146]

Antihypertensive medication may modulate the plasma levels of adiponectin. Thiazide diuretics seem to reduce plasma adiponectin levels.[147] Another diuretic, indapamide, also reduces plasma adiponectin concentration.[148] Beta-adrenergic blockers reduce or have no effect on plasma adiponectin levels.[147–149] Calcium channel blockers increase or have no effect on plasma adiponectin concentrations.[147,149–151] Blocking the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin receptor 1 blockers consistently increase plasma adiponectin levels.[126,147,149,152–154] Spironolactone has also been reported to increase plasma adiponectin in type 2 diabetic patients with nephropathy.[155] No human studies of eplerenone or

aliskiren have been published. The α-adrenergic blocker doxazosin has also been shown to increase plasma adiponectin levels.[149] Overall, the adiponectin-raising effects of antihypertensive agents appear to parallel their effects on insulin sensitivity.[147,149] Among these antihypertensives, so far, only losartan has been shown to increase total and HMW adiponectin.[156]

Hypoadiponectinemia is related closely to obesity, T2DM, dyslipidemia and hypertension. These metabolic abnormalities are not only the key components of the metabolic syndrome, but also the major risk factors for cardiovascular diseases.[77] Therefore, we will next review the relationship between blood adiponectin and coronary, cerebral and peripheral artery diseases, congestive heart failure (CHF) and cardiac arrhythmia.

Plasma adiponectin and coronary artery disease (CAD)

Plasma adiponectin was first shown to be lower in patients with CAD by Ouchi et al in 1999.[157] The association between low plasma adiponectin and CAD, disease extent or outcomes has been demonstrated not only in cross-sectional studies,[157–161] but also in prospective longitudinal follow-up studies.[162–166] For example, in a follow-up study of male health professionals, the subjects with higher adiponectin levels had a significantly reduced risk of myocardial infarction, even after correction for risk factors, such as LDL and HDL levels, BMI, history of diabetes and hypertension and high-sensitivity C-reactive protein at baseline.[167] Some other studies, however, have not found a predictive value for future risk of CAD.[168,169] A meta-analysis has suggested a significant association, but the effect was relatively moderate compared with that in previous studies.[170]

HMW adiponectin is lower in men with CAD, but not in women.[171] In a follow-up study, HMW adiponectin has been shown to predict cardiovascular events in men.[172] HMW adiponectin is also associated with extent of CAD in men.[173] However, negative results have also been reported.[174–177] Whether gender is an issue or not in this regard remains to be clarified. Furthermore, whether adiponectin plays a specific role at certain specific stages of CAD pathogenesis needs to be investigated more thoroughly.

Plasma adiponectin and stroke and peripheral artery disease (PAD)

Lower blood adiponectin levels have been reported to be associated with increased risk of ischemic stroke and increased mortality after first stroke event.[178,179] On the other hand, some other studies have not confirmed the value of adiponectin in relation to cerebrovascular events.[180–182] Plasma adiponectin has also been shown to be inversely related to PAD, estimated by ankle–brachial index in hemodialysis patients.[183] So far, no study has addressed the role of HMW adiponectin isoforms in cerebrovascular disease or PAD. Furthermore, no human investigation of the effects of pentoxyphylline or cilostazol, which are commonly used in treating PAD in clinical practice, on plasma adiponectin levels has been reported. However, a novel selective serotonin 2A receptor antagonist, sarpogrelate, has been investigated in non-diabetic and non-medicated diabetic patients with PAD.[184] It was shown to enhance insulin sensitivity and increase plasma adiponectin.

Plasma adiponectin and CHF and cardiac arrhythmia

The first human study regarding the role of adiponectin in CHF was surprising.[185] It showed that high blood adiponectin was a predictor for mortality in CHF, independent of other risk factors. It was suggested that high adiponectin in CHF was a sign of physical wasting. Other studies have also demonstrated that higher adiponectin is an independent predictor for mortality and/or hospitalization in patients with CHF.[186–189] In cross-sectional studies, patients with CHF had higher plasma adiponectin levels and decreased lean body mass.[188,190,191] However, in a longitudinal follow-up study, in which insulin resistance was reported to be an independent risk factor for CHF, plasma adiponectin was not a predictor for

CHF.[192] In one study that has surveyed the role of HMW adiponectin, it was concluded that total, rather than HMW adiponectin was valuable in predicting mortality in CHF.[193] In many studies, plasma adiponectin level appears to parallel the level of natriuretic peptide.[185,186,188,189,191,194,195] Moreover, infusion of carperitide (a natriuretic peptide) in CHF patients increased their plasma total and HMW adiponectin levels.[196]

Cardiac arrhythmia is a common condition in patients with cardiovascular diseases. It has been reported that plasma adiponectin levels are higher in chronic atrial fibrillation (AF) than in paroxysmal AF and controls.[197] The plasma adiponectin levels are correlated with the collagen metabolism marker, carboxy-terminal telopeptide of collagen I, but not with type III pro-collagen-N-peptide.[197] So far, there has been no report of adiponectin with regard to ventricular arrhythmia, syncope, fainting or sudden death.

Conclusion

Substantial evidence has revealed the significance of adiponectin in human health and diseases. The underlying molecular mechanisms have provided us with clues to the intricate relationship between adiponectin and pathogenesis. Alterations in blood adiponectin concentration seem to be a useful biomarker for obesity, DM, dyslipidemia, hypertension, and even subsequent cardiovascular diseases. We summarized the relationship of blood adiponectin with cardiometabolic disorders in this review. The proposed natural history is depicted in the Figure. Hypoadiponectinemia may be caused by obesity-induced insulin resistance in the adipose tissue, as previously proposed.[13] Hypoadiponectinemia may contribute secondarily to insulin resistance in other peripheral tissues, such as liver and skeletal muscle.[13] As a result, T2DM, dyslipidemia, hypertension, metabolic syndrome and

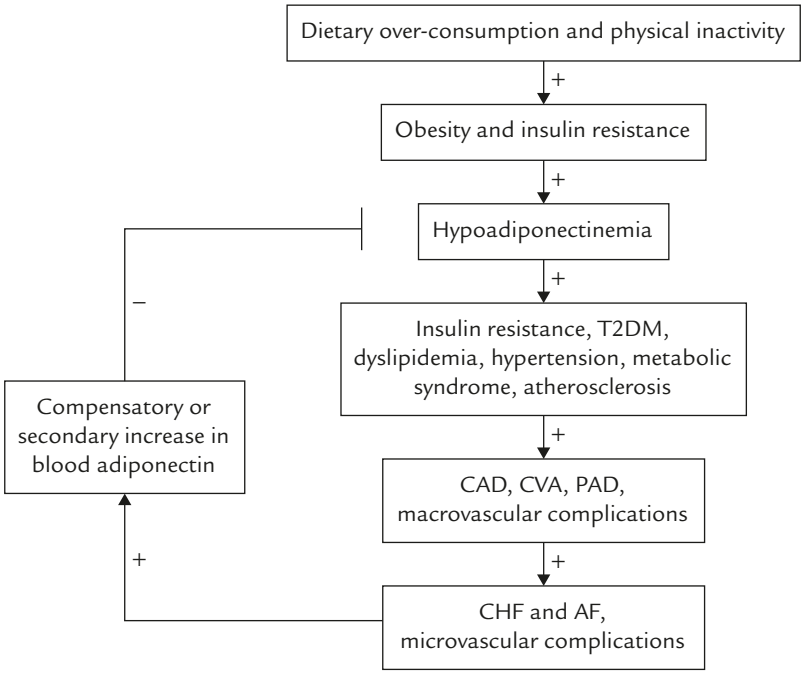

Figure. Schematic diagram depicting the proposed natural course of blood adiponectin levels in relation to cardiometabolic disorders reviewed in this article. The arrows indicate the proposed time sequence and may not necessarily imply cause–effect relationships. The "+" signs indicate a positive association. The "–" sign indicates a negative association. Hypoadiponectinemia is proposed to be caused by obesity-induced insulin resistance in the adipose tissue.[13] Hypoadiponectinemia in turn induces insulin resistance in other tissues. As the result of certain microvascular complications, such as nephropathy and CHF, the plasma levels of adiponectin may rise. T2DM = type 2 diabetes mellitus; CAD = coronary artery disease; CVA = cerebrovascular accident; PAD = peripheral artery disease; CHF = congestive heart failure; AF = atrial fibrillation.

accelerated atherosclerosis occur. These conditions may lead to subsequent macro- and microvascular complications, and CHF and arrhythmia may follow. As a result of CHF, AF or nephropathy, compensatory or secondary rise in blood adiponectin may occur later (Figure). The mechanisms of this rise in blood adiponectin levels remain unclear. It may be caused by reduced renal clearance of adiponectin, disease-related weight loss, or increased ectopic secretion of adiponectin from the myocardium. If the rise in blood adiponectin is proven to be beneficial, we do not have to wait until late clinical events occur. Non-pharmacological and pharmacological modulations of blood adiponectin levels may be promising for ameliorating the related disorders in the earlier stages. Through more comprehensive studies, we believe that the true clinical value and the mystery of the pathogenic mechanisms of adiponectin in human diseases will be unraveled in the near future.

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